AMENDMENTS TO THE CLAIMS

1. (Currently Amended) A method of identifying a subject predisposed to ischemic stroke, ~~the~~ wherein said method ~~including the step of~~comprises:

determining a rate of release of tissue plasminogen activator in a subject; and

identifying a subject predisposed to ischemic stroke by a reduction in the rate of release of tissue plasminogen activator in the subject

~~identifying a mutation in the subject that reduces the release rate of tissue plasminogen activator~~.

2. (Currently Amended) [[A]]The method according to claim 1, wherein the ischemic stroke is a lacunar stroke.

3. (Currently Amended) [[A]]The method according to ~~claims 1 or 2~~claim 130, wherein the mutation is located in the tissue plasminogen activator locus.

4. (Currently Amended) [[A]]The method according to claim 3, wherein the mutation is located in an upstream region of the tissue plasminogen activator locus.

5. (Cancelled)

6. (Currently Amended) A method according to ~~any one of claims~~claim 3 ~~to 5~~, wherein the mutation is located in both alleles of the tissue plasminogen activator locus.

7. (Currently Amended) [[A]]The method according to ~~claim 6~~claim 3, wherein the mutation is a cytosine to thymine mutation at position –7351 of the upstream region of the tissue plasminogen locus.

8. (Cancelled)

9. (Currently Amended) [[A]]The method according to ~~any one of claims 1 to 8~~claim 130, wherein the identification of the mutation includes detection of the mutation by ~~hybridisation~~ hybridization of nucleic acid isolated or derived from the subject to a reporter nucleic acid.

10. (Currently Amended) A method of identifying a subject predisposed to small vessel occlusion, ~~the~~wherein said method ~~including the step of~~ comprises:

determining a rate of release of tissue plasminogen activator in a subject; and

identifying a ~~mutation in the~~ subject ~~that reduces the~~ predisposed to small vessel occlusion by a reduction in the rate of release ~~rate~~ of tissue plasminogen activator in the subject.

11. (Currently Amended) [[A]]The method according to claim ~~10~~132, wherein the small vessel occlusion manifests clinically as a disease or condition selected from the group consisting of: lacunar stroke, dementia, ischemic heart disease, ~~(including~~ ischemic cardiomyopathy~~)~~, peripheral vascular disease, disseminated intravascular coagulation, small vessel vasculitis, ischemic neuropathy, ischemic retinopathy, ischemic gastropathy, ~~(including~~ small and large bowel ischemia~~)~~, diffuse pulmonary embolism, and vascular impotence.

12. (Cancelled)

13. (Currently Amended) [[A]]The method according to ~~any one of claims 10 to 12~~claim 132, wherein the mutation is located in the tissue plasminogen activator locus.

14-16. (Cancelled)

17. (Currently Amended) [[A]]The method according to claim ~~16~~132, wherein the mutation is a cytosine to thymine mutation at position –7351 of the upstream region of the tissue plasminogen locus.

18-34. (Cancelled)

35. (Currently Amended) [[A]]The method according to claim ~~35~~132, wherein the mutation is in both alleles of the tissue plasminogen activator locus.

36-37. (Cancelled)

38. (Currently Amended) [[A]]The method according to ~~any one of claims 30 to 37~~claim 132, wherein the identification of the mutation includes detection of the mutation by ~~hybridisation~~ hybridization of nucleic acid isolated or derived from the subject to a reporter nucleic acid.

39. (Cancelled)

40. (Currently Amended) [[A]]The method according to claim ~~39~~133, wherein the disease or condition is ~~a~~selected from the group consisting of: lacunar stroke, dementia, ischemic heart disease, ~~(including~~ ischemic cardiomyopathy~~)~~, peripheral vascular disease, disseminated intravascular coagulation, small vessel vasculitis, ischemic neuropathy, ischemic retinopathy, ischemic gastropathy, ~~(including~~ small and large bowel ischemia~~)~~, diffuse pulmonary embolism, ~~or~~and vascular impotence.

41-48. (Cancelled)

49. (Currently Amended) A method of treating and/or treating a disease or condition associated with small vessel occlusion in a subject, ~~the~~wherein said method ~~including the step of~~comprises:

administering to the subject a therapeutically effective amount of an agent that increases the rate of release of tissue plasminogen activator in the subject.

50. (Currently Amended) [[A]]The method according to claim 49, wherein the disease or condition is selected from the group consisting of: a lacunar stroke, dementia, ischemic heart disease, ~~(including~~ ischemic cardiomyopathy~~)~~, peripheral vascular disease, disseminated intravascular coagulation, small vessel vasculitis, ischemic neuropathy, ischemic retinopathy, ischemic

gastropathy, ~~(including~~ small and large bowel ischemia~~)~~, diffuse pulmonary embolism, ~~or~~and vascular impotence.

51-114. (Cancelled)

115. (Currently Amended) An isolated nucleic acid ~~with~~comprising:

(i) ~~one or more base substitutions in~~ the sequence according to SEQ ID ~~No.~~NO: 3, or

(ii) SEQ ID NO:4, or

(iii) a RNA equivalent of (i) or (ii); or

(iv) SEQ ID NO:3 having one or more nucleotide substitutions

(v) SEQ ID NO:4 having one or more nucleotide substitutions;

wherein the isolated nucleic acid ~~has~~sequences having one or more nucleotide substitutions are at least 80% ~~homology~~ homologous to SEQ. ID ~~No.~~NO:3 or SEQ ID NO:4, or

wherein the isolated nucleic acid having one or more nucleotide substitutions hybridizes with the complement of SEQ ID NO:3 or SEQ ID NO:4 under stringent hybridization conditions comprising hybridization at 6xSSC at 42 °C and washing in 2xSSC at 20 °C~~or RNA equivalent thereof~~.

116-129. (Cancelled)

130. (New) The method according to claim 1, wherein said method further comprises:

determining a reduced rate of release of tissue plasminogen activator in the subject by identifying a mutation in the subject that reduces the rate of release of tissue plasminogen activator in the subject.

131. (New) The method according to claim 1, wherein the method is used to (i) identify a subject suitable for intervention to prevent and/or treat ischemic stroke; and/or (ii) determine the risk of ischemic stroke occurring in a subject.

132. (New) The method according to claim 10, wherein said method further comprises:

determining a reduced rate of release of tissue plasminogen activator in the subject by identifying a mutation in the subject that reduces the rate of release of tissue plasminogen activator in the subject.

133. (New) The method according to claim 10, wherein the subject having a reduced rate of release of tissue plasminogen activator is suitable for (i) intervention to prevent and/or treat ischemic stroke; and/or (ii) intervention to prevent and/or treat a small vessel occlusion; and/or (iii) intervention to prevent and/or treat a disease or condition associated with small vessel occlusion.

134. (New) The method according to claim 49, wherein the agent is monosodium [2-(6-hydroxynaphthalen-2-yl)-6-methyl-pyrimidin-4-yloxy]acetate dihydrate (JTV-926) or other bradykinin agonist.